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Cancer morbidity in rheumatoid arthritis

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SUMMARY A consecutive series of 489 patients with rheumatoid arthritis seen at the centre was studied to determine their cancer morbidity. Overall the 36 cancers diagnosed in the series between 1964 and 1981 were not significantly in excess of the expected number, but there was a highly significant excess of tumours of the reticuloendothelial system. The excess was mainly due to 6 observed cases of lymphoma. We conclude that there is a highly significant association between rheumatoid arthritis and the subsequent development of lymphoproliferative malignancy in this series.

An increased incidence of lymphoproliferative malignancy (LPM) has been suggested to occur in various connective tissue diseases. These include Sjögren's syndrome[1 2] rheumatoid arthritis (RA),[3–5] and systemic lupus erythematosus.[6 7] RA is the commonest of these diseases and has been the focus of attention. However, the evidence that the risk of malignancy is increased in RA is conflicting. One large Scandinavian series[5] has reported a highly significant association (relative risk = 2·2) between RA and cancers of the reticuloendothelial system (RES). However, not all centres have found this,[8–10] and there is considerable uncertainty as to whether cancer morbidity is increased in RA. In view of this uncertainty and the need to quantitate any increased risk due to the iatrogenic dangers of therapy with cytotoxic drugs[11] we have studied this problem further. To eliminate problems of diagnostic variation we have investigated patients under the care of only one physician (C.F.H.). To minimise the problem of unrecorded malignancy the study has been undertaken in a region with a long established cancer registry. The incidence of cancer in a consecutive series of patients with RA from the West Midlands Region has been compared with the incidence of cancers in the West Midlands population to establish whether RA patients in general are at an increased risk of developing cancer at any site or of LPM in particular.

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Patients and methods

A consecutive series of 489 inpatients and outpatients with RA (American Rheumatism Association criteria) was seen by rheumatology staff of the Queen Elizabeth Hospital, Birmingham, between 1964 and 1978. They were all under the care of one physician (C.F.H.). The case notes were reviewed and the following items of data abstracted; name, address, date of birth, sex, date of onset of symptoms, hospital first attended, date first seen, rheumatoid factor status, gold therapy, and steroid therapy.

Patients were traced up to 31 December 1981 through hospital records, the National Health Service Central Register, the Birmingham Cancer Registry, and general practitioners. Copies of death notifications were obtained from those patients who had died, and patients who had been diagnosed with cancer were identified from the Cancer Registry records. The site of cancer was coded to the 8th revision of the International Classification of Diseases (ICD).[12] Person-years at risk were computed from the date first seen at the hospital after 1 January 1964 (this being the date when the register of cases was first compiled) to the termination date (31 December 1981) or to death if that occurred first. We computed age-, sex-, and site-specific incidence rates for cancer from the registry data, taking into account calendar period and incompatibilities between ICD (7th revision)[13] and ICD (8th revision). By applying the rates to the appropriate age- and sex-specific person-years at risk the numbers of cancers that might be expected to occur during the period of observation were computed.

Results

The status of 448 patients (91·6%) was established of whom 15 patients (3·1%) were only partially traced. Information was insufficient for tracing or analysis in 41 cases (8·4%). Age-distribution by sex for the 448 patients included in the analysis are shown in Table 1. 26% of the patients were seen in hospital before 40 years of age. Rheumatoid factor status was known for 421 patients (94%), of whom 252 (60%) were seropositive. A complete drug history was not available for every patient. However, the use of gold and steroids was known for 424 and 438 patients respectively. Among these patients 36% had received gold, 51·8% steroids, and 25% had neither. In terms of the total series (448 patients) 50·7% received steroids and 34·2% gold. The other frequently used second-line drugs were chloroquine (7·8%) and penicillamine (6·3%). Dapsone was used in 7 cases, sulphasalazine (Salazopyrin) in 5 cases, and azathioprine in 2 cases. Single drug therapy was recorded for 37·4% patients, and the use of combination or multiple sequental drugs was known for 32·6% of patients. Analgesics and aspirin (and 'aspirin-like' drugs) were given to almost all patients, and the extent of their prescription in general practice is unknown.

Overall the 36 cancers diagnosed in the series within the period of review were not significantly in excess of the expected number (Table 2). The observed and expected numbers for individual sites have been grouped by main anatomical systems according to categories of the International Classification of Disease (8th revision). Only for cancers of the reticuloendothelial system was the observed number significantly in excess of the expected number ($p<0·001$). No other significant deviation from expectation was observed, and, when cancers other than those of the RES were combined, the observed and expected number corresponded very closely (Table 3). The highly significant excess of RES cancers (relative risk = 8·0; 95% confidence limits: 3·7 to 15·2) was apparent in both men and women (Table 4) and was due mainly to 6 observed cases of lymphoma (relative risk 23·0; 95% confidence limits: 8·4 to 50·1). Two patients were diagnosed with lymphosarcoma within 1 year of their first attendance at hospital. If they are excluded from the analysis the resultant 15·5-fold risk still remains highly significant ($p<0·001$).

The 2 cases of leukaemia (1 chronic lymphatic and 1 acute monocytic) in women represented an excess of only borderline significance ($p<0·05$) and when all RES cancers were separated into 'lymphoma' and 'other RES' cancers the apparent 3·4-fold excess in the latter group did not acheive the 5% significance level (Table 5).

When all 6 observed cases of lymphoma were included in the analysis a very high relative risk was found in the first 5 years after first attendance (Table 6). Thereafter the cumulative relative risk was of the order of 25-fold. On excluding the 2 cases in the first year the cumulative risk increased over time. For other RES tumours combined the cumulative risk was comparatively constant over time. The difficulty of relating interval from date first seen with onset is shown in Table 7, where the 6 cases of lymphoma are arranged by increasing interval from onset. The 2 lymphosarcomas, diagnosed within one year of first

Table 1 *Distribution of the series of 448 patients with rheumatoid arthritis by sex and by age when first seen at hospital*

Age	*Males*	*Females*	*Total*	*%*
<20	9	13	22	(4·9)
20–29	9	27	36	(8·0)
30–39	23	37	60	(13·4)
40–49	33	78	111	(24·8)
50–59	48	77	125	(27·9)
60+	33	61	94	(21·0)
Total	155	293	448	

Table 2 *Cancer morbidity in 448 male and female patients with rheumatoid arthritis*

Site of Cancer	*ICD 8th rev.*	*Expected No. (E)*	*Observed No. (O)*	*O/E*	*p*
All sites	140–208	27·57	36	1·3	—
Mouth + oropharynx	140–148	0·47	0	—	—
Digestive system	150–157	6·79	8	1·2	—
Respiratory system	160–162	4·92	4	0·8	—
Skin	172–173	2·90	2	0·7	—
Reproductive system	174–187	8·02	8	1·0	—
Urinary system	188–189	1·37	1	0·7	—
Reticuloendothelial system	200–208	1·13	9	8·0	***
Remainder		1·97	4	2·0	—

***$p<0·001$.

Table 3 *Cancer morbidity: reticuloendothelial system (RES) and all other sites combined (remainder)*

Site of cancer	*ICD 8th rev.*	*E*	*O*	*O/E*	*p*
All sites	140–208	27·57	36	1·3	—
RES	200–208	1·13	9	8·0	***
Remainder		26·44	27	1·0	—

***$p<0·001$.

attendance, showed only a short interval from onset, whereas those with the longer intervals were of the histiocytic (reticulosarcoma) type.

Table 4 *Cancer morbidity: reticuloendothelial system (RES)*

Site of Cancer	*ICD 8th rev.*	*Sex*	*E*	*O*	*O/E*	*p*
RES	200–208	M	0·49	4	8·2	**
		F	0·64	5	7·8	***
		Total	1·13	9	8·0	***
Lymphoma	200	M	0·11	3	27·3	***
		F	0·15	3	20·0	***
		Total	0·26	6	23·0	***
Hodgkin's disease	201	M	0·06	1	16·7	—
		F	0·08	0	—	—
		Total	0·14	1	7·1	—
Other reticuloses	202	M	0·04	0	—	—
		F	0·05	0	—	—
		Total	0·09	0	—	—
Myelomatosis	203	M	0·08	0	—	—
		F	0·11	0	—	—
		Total	0·19	0	—	—
Leukaemia	204–207	M	0·18	0	—	—
		F	0·23	2	8·7	*
		Total	0·41	2	4·9	—
Polycythaemia	208	M	0·02	0	—	—
		F	0·02	0	—	—
		Total	0·04	0	—	—

*p<0·05. **p<0·01. ***p<0·001.

Table 5 *Cancer morbidity: lymphoma versus other RES*

Site of cancer	*ICD 8th rev.*	*E*	*O*	*O/E*	*p*
RES	200–208	1·13	9	8·0	***
Lymphoma	200	0·26	6(4)†	23·0(15·44)†	***(***)
Other	201–208	0·87	3	3·4	—

***p<0·001.
† Excluding 2 cases diagnosed within one year from date first seen at hospital.

Table 7 *Interval to diagnosis of cancer from (1) onset of RA and (2) date first seen*

Case no.	*Sex*	*Histology*	*Interval from: (1) onset*	*(2) date first seen after 1 Jan 1964*
317	M	Lymphosarcoma	3y 0m	0y 0m
506	M	Lymphosarcoma	3y 9m	0y 6m
104	M	Histiocytic reticulosarcoma	5y 6m	5y 2m
467	F	Immunoblastic lymphoma	17y 0m	14y 0m
325	F	Histiocytic lymphoma	17y 6m	11y 8m†
412	F	Histiocytic lymphoma	18y 1m	1y 1m

†From 1 January 1964 but first seen in 1959, i.e. 16y 6m.

Discussion

Bias in selection makes for uncertainty in any analysis of clinical series and is probably of even more importance when considering chronic disease. In the context of RA, patients might be preferentially referred with more severe or unremitting disease, with uncertain or more obscure diagnoses, or even for conditions unrelated to RA, but because the diagnosis of RA has already been made they would present at the rheumatology clinic. In an attempt to minimise one area of bias the computation of person-years was started from 1 January 1964. Although some patients had been seen before this date, they represent a survivor population of a previous cohort, some of whose numbers may have died from cancer or other conditions and who would therefore be unidentifiable.

The second area of uncertainty relates to preferential referrals for cancer to the rheumatology clinic. Patients who first attend the clinic late in the course of the disease may be referred because of the complications of RA and possibly for unrelated conditions

Table 6 *Cancer morbidity: cumulative numbers of lymphosarcomas and other RES cancers over time (from date first seen at hospital after 1 January 1964)*

Interval from date first seen	*Lymphoma (ICD 200)*							*RES—other (ICD 201—208)*			
(YEARS)	E	O	O/E	p	O′	O/E	p	E	O	O/E	p
0–4	0·09	3	33·3	***	1	11·0	—	0·30	1	3·3	—
5–9	0·18	4	22·2	***	2	11·4	*	0·59	2	3·4	—
10–14	0·24	6	25·0	***	4	16·5	***	0·81	3	3·7	*
15–19	0·26	6	23·1	***	4	15·5	***	0·87	3	3·4	—

*p<0·05. ***p<0·001.
E = expected number. O = total observed number. O′ = observed number excluding cancers occurring within one year of date first seen.

including cancer. For this reason the case notes for all patients who were diagnosed with cancer within one year of attendance were reviewed. Two patients with lymphosarcoma fall in to this category, and although no definite basis for exclusion could be determined the analysis was repeated to show their effect on the estimates of relative risk. One patient with a suspected bronchial carcinoma was excluded from the analysis because he was found to have carcinomatosis at first attendance, and it seemed likely that this was the cause of his referral rather than any symptom of his RA. The remaining cancers discovered within the first year were considered to be incidental findings and were not instrumental in bringing the patient to hospital. Thus, although they may have been diagnosed relatively earlier than a cancer in patients without RA, they were valid inclusions in the observed numbers. In addition one case of chronic lymphatic leukaemia was excluded because the diagnosis had been made before 1964.

Another possible source of inaccuracy in the analysis might arise from the exclusion of patients for whom insufficient information was available. Some of these patients were in fact traced through registry records. To have included them in the analysis would have served only to introduce bias in selection for cancers.

The assumption that there was no undue bias in selection for cancer in the cases which remained for analysis is supported in several ways: first, the observed and expected numbers of cancers for sites other than RES corresponded closely; secondly, RES cancers were still significantly in excess after the exclusion of 2 cases; and, thirdly, when the analysis was restricted to patients who had presented within 5 years of *onset* of RA, RES cancers were significantly in excess in this group with the 2 lymphomas in the first year included ($O = 7$; $E = 0{\cdot}637$; $RR = 11{\cdot}0$; $p<0{\cdot}001$) and without ($O = 5$; $E = 0{\cdot}637$; $RR = 7{\cdot}8$; $p<0{\cdot}001$) (RR = relative risk).

Terminology may be misleading. Isomaki *et al.*[5] considered the risk of LPM but did not indicate whether the observed leukaemias were of lymphoid origin. It is also possible that some of the excess risk of leukaemia in the series could be attributed to radiotherapy in patients with ankylosing spondylitis who were also included.

In our analysis we have not been able to distinguish between lymphoid and nonlymphoid elements in the expected numbers for leukaemia. We have therefore referred to RES cancers in general. However, among the group labelled 'RES-other' one case of Hodgkin's lymphoma and one of chronic lymphocytic leukaemia were observed. Our results therefore support the previous studies which have suggested an association between RA and LPM.[3-5] The failure of other studies to show this effect probably results from their methodology and, in some, too brief a follow-up. However, in an attempt to investigate this problem further we have reviewed in detail a series of 20 patients with RA and LPM, and the results are published in a second paper.

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